Author Information:

Itamar Ronen, PhD
Department of Anatomy and Nerurobiology
715 Albany Street, L-1004
Boston University School of Medicine
Boston MA 02118

Phone: 617-414-2360
Fax: 617-414-2371
Email: Itamar@bu.edu

Cytoarchitectonic MRI: Can MRI Be Used to Quantify Neural Tissue?

Itamar Ronen and Dae-Shik Kim
Dept. of Anatomy and Neurobiology, Boston University School of Medicine, Boston MA 02118, USA

Abstract: What should be done in order to obtain quantitative cytoarchitectonic neuroanatomical data, such as cell density, average axonal diameter and percent myelination from MRI data? What are the obstacles that we have to overcome in order to achieve this goal, and what are the possible approaches that we should explore – on the acquisition, modeling and on the post-processing level? Here we try to summarize what efforts have been done in this direction and explore some of the possible approaches that can be used to bring MRI to the level of an "indirect neuroanatomical microscope".

Introduction: Microscopic properties of neural tissue, such as cell size and geometry, cell density, membrane properties and macromolecular content all have visible and measurable impact on a plethora of MRI methods. Mounting amount of evidence show a robust link between diffusion properties of water, such as fractional anisotropy (FA) apparent diffusion coefficient (ADC) and displacement distribution functions on the one hand, and tissue geometry on the other. Magnetization transfer (MT) methods create a contrast related to exchange sites on heavy macromolecules such as the myelin sheath – an essential ingredient in neural tissue structure. Relaxation data of all kinds (T_1, $T_{1\rho}$, T_2, T_2^*) are also intimately linked to the way water interacts with its surroundings in tissue – whether through subtle variations in mobility, chemical composition or magnetic susceptibility of the surrounding medium. More recently – inter- and intramolecular multiple quantum filtered (MQF) imaging have been used to shed light on order in biological structures[1] and on compartmentation in tissue[2, 3]. Yet – a robust, *quantitative* connection between MRI observables and basic cytoarchitectonic parameters such as cellular density, average cellular size or axonal diameter, intra/extracellular compartmental fractional volumes and degree of myelination does not exist. The difficulty in establishing a quantitative relationship between MR observables and cytoarchitectonic parameters can be attributed to various reasons, among which: (a) the relatively low spatial resolution of MRI, in particular in the clinical setting; (b) the fact that the observable in most cases are the *mobile* water molecules and not the structures *per se*; (c) the lack of one-to-one correspondence between the MR observable (relaxation time, diffusion property) and a single population of spins that represents a cytoarchitectonic unit or compartment. A strive to establish a quantitative link between MRI and cytoarchitecture, or "MRI as a microscope" should be a most rewarding one, since no tool like MRI has the advantage of being non invasive on the one hand, and being able to provide wealth of information linked to microscopic tissue structure on the other. In order to solicit a lively discussion, few general approaches are herein presented, and to each is appended a short wish list, or a "what's need to be done" item to bring MRI closer to becoming a viable quantitative cytoarchitectonic tool.

Possible Approaches:

(a) ***The direct approach***: the possibility of obtaining *direct* cytoarchitectonic data from MRI has been explored in several directions: q-space analysis, which links the root mean square (RMS) of the displacement distribution function *per pixel* with diffusion-weighted MR data, yields information that is closely related to the typical size of tissue compartments[4]. In an altogether different type of experiment, intermolecular DQF-MRI has been shown to provide data that depends on the typical compartment size in trabecular bone[2].

(b) ***The multimodal approach (acquisition)***: an important step towards "cytoarchitectonic MRI" is targeting of a specific population of spins and connecting it with an MRI observable. Since in most cases there is no one-to-one connection between spin population of a specific compartment and an MRI observable, a possible approach is to combine several measurements in one experimental session such that the combined results provide data whose source can be unequivocally attributed to either *one* or *several* specific tissue compartment. The relaxation-relaxation and diffusion-relaxation 2D experiments are fine examples of this approach, and have been successfully applied to porous media[5] and isolated cells[6]. The resulting *several* peaks in the 2D "spectrum" are tentatively attributed to various spin population within the medium, and can thus be explored as to their "affiliation" in the realm of tissue structure.

(c) ***The compartment selective approach***: Direct selection of a spin pool that resides in a specific compartment can be also an initial step towards cytoarchitectonic exploration of tissue. The ultra-short T_2 component has been shown to be generated by the "myelin water" in myelinated white matter[7]. Analysis of DQF spectra has enabled the identification of three compartments in isolated nerve[8]. Targeting non-water compounds can also easily focus the measurement on a specific compartment. Several examples involve diffusion measurements on metabolites[9] or exogenous markers[10]. MQF-spectra of quadrupolar nuclei (e.g. ^{23}Na) showed selectivity to the intracellular space[3]. Contrast agents that can be delivered selectively to the intracellular space can also allow for selective targeting of properties of either the intra- or extracellular spaces.

(d) ***The multimodal approach (post-processing)***: A different approach, which has not been implemented yet, is a multimodal *phenomenological* approach. Data relevant to neural cytoarchitecture can be acquired using several MR modalities, e.g. T_2 maps, DTI and q-space data, MTC maps and chemical shift imaging (CSI) maps. Each "hyper-pixel" in this combined multimodal data set corresponds, *perhaps uniquely*, to one or a set of cytoarchitectonic variables. The goal is to establish, perhaps in a semi-empirical way, a connection between the multimodal data and the cytoarchitectonic variables.

(Very non complete list of) References: 1. Tsoref, L., et al., Magn Reson Med, 1998. **40**(5): p. 720-6. 2. Capuani, S., et al., Solid State Nucl Magn Reson, 2004. **25**(1-3): p. 153-9. 3. Navon, G., Magn Reson Med, 1993. **30**(4): p. 503-6. 4. Assaf, Y., A. Mayk, and Y. Cohen, Magn Reson Med, 2000. **44**(5): p. 713-22. 5. Callaghan, P.T., S. Godefroy, and B.N. Ryland, Magn Reson Imaging, 2003. **21**(3-4): p. 243-8. 6. Silva, M.D., et al., J Magn Reson, 2002. **156**(1): p. 52-63. 7. MacKay, A., et al., Magn Reson Med, 1994. **31**(6): p. 673-7. 8. Seo, Y., et al., Magn Reson Med, 1999. **42**(3): p. 461-6. 9. Assaf, Y. and Y. Cohen, NMR Biomed, 1999. **12**(6): p. 335-44. 10. Yi, L., J. Neil, and J.J.H. Ackerman, NMR in Biomedicine, 1995. **8**(5): p. 183-9.